REMARKS

The first paragraph of the specification has been amended to recite the Patent Nos. of the priority cases.

Formal drawings (FIGURE 1A-G and FIGURE 2A-F) have been prepared and are being submitted imminently. The specification has been amended to refer to multiple views as they appear in the formal drawings (*i.e.*, views A-G of FIGURE 1 and A-F of FIGURE 2). The specification has also been amended (*i.e.*, at page 35) to recite textual material which appeared in informal FIGURE 2 as-filed.

No new matter has been added to the application. Accordingly, it is respectfully requested that the above amendments be entered.

Claims 106-108 and 115-134 were pending in the instant application. Claims 116, 119 and 134 have been cancelled. Claims 106-108, 115, 117-118, 120-129 and 131-133 have been amended. New claims 135-143 have been added. Accordingly, claims 106-108, 115, 117-118, 120-133 and 135-143 will be pending in the application upon entry of the instant amendment. Support for the claim amendments and new claims can be found throughout the specification and claims as originally filed. No new matter has been added.

Attached hereto is Appendix A, captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". The attached Appendix includes a marked-up version of the changes made to the claims by the current amendment.

Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicants' invention to

expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or in a separate application(s).

Claim Objections

The Examiner has objected to claims 125-126 as being substantial duplicates. Claim 125 is directed to a method for identifying MRP-β modulators that involves assaying the level of expression of the MRP-β, wherein assaying the level of MRP-β involves assaying the amount or rate of production of MRP-β *nucleic acid* in a test cell. Claim 126 is directed to a method for identifying MRP-β modulators that involves assaying the level of expression of the MRP-β, wherein assaying the level of MRP-β involves assaying the amount or rate of production of MRP-β *polypeptide* in a test cell.

Applicant is unaware of the basis for the instant claim objection and respectfully submits that claims 125-126 are clearly directed to distinct subject matter. Should the Examiner maintain the claim objection after reconsideration, clarification of the basis of the rejection is requested.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 106-108 and 115-134 are rejected under 35 U.S.C. 112, second paragraph, because, according to the Examiner, the claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, the Examiner states that the "metes and bounds" of claims 106-108 and 115-134 cannot be determined due to the recitation of the abbreviation "MRP-β".

Claims 116, 119 and 134 have been cancelled, rendering the rejection moot with respect to these claims. With respect to claims 106-108, 115, 117-118 and 120-133, Applicant respectfully traverses the rejection. It is Applicant's position that the specification is replete with teachings as to what is meant by the term MRP-β. In particular, the specification teaches that MRP-β is a new member of an art-recognized class of multidrug resistance-associated polypeptides (MRPs) having a distinct structural and functional characteristic as well as a distinct cellular and tissue expression pattern. The specification teaches that MRP-β polypeptides include certain MRP-β homologues and variants, for example, at the paragraph spanning pages 10-11. Although it is Applicant's position that a skilled artisan would understand what the term MRP-β is intended to encompass, Applicant has amended the pending claims to provide specific recitation of reference MRP-β molecules (*i.e.*, specific MRP-β nucleic acid molecules and/or polypeptides) in order to expedite prosecution of the instant case. In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The Examiner further states that the claims are indefinite in reciting that a "detectable fluctuation" of MRP-β expression or activity indicates that a candidate is an MRP-β modulator. The Examiner indicates that the claims should recite "what is to be measured in order to determine that a fluctuation has occurred" and suggests that the claims recite detecting fluctuation in the "presence" or "absence" of a candidate compound. Applicant traverses. It is Applicant's position that a skilled artisan would clearly understand what constitutes measuring a detectable fluctuation in expression or activity. The skilled artisan is free to compare expression or activity in the presence of

the candidate compound to any suitable control known in the art including, but not limited to, cells in the absence of compound, wells, vessels, plates, chips and the like in the presence of control solutions, *e.g.*, buffers, media, and/or solvents, control positive or negative values, known compounds of particular efficacy, etc. To limit the determination of a detectable fluctuation in expression or activity to comparing values in the presence or absence of candidate compound would unduly restrictive, as the skilled artisan can readily envision many art-recognized means for determining a detectable fluctuation. In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The Examiner further states that the claims are indefinite over the recitation of the term "substrate". The Examiner states that "[i]t is unclear from the disclosure whether the claimed substrate is equivalent to a cytotoxin or whether a cytotoxin is one species of the claimed genus of substrates". Applicant traverses. It is Applicant's position that the specification is clear in teaching that MRP-β polypeptides of the invention, as well as other members of this class of transporters (*e.g.*, other ABC transporters), can transport substrates including not only cytotoxins, but derivatized cytotoxins, cytotoxin metabolites, and the like. To limit the term substrate to a "cytotoxin" would be unduly restrictive, as the skilled artisan can readily envision the substrates transported by the polypeptides of the invention. In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The Examiner rejects claims 115 and 116 as indefinite over the recitation of "the nucleic acid molecule of SEQ ID No: 2". Applicant respectfully submits that the instant amendment of claim 115 and cancellation of claim 116 renders this rejection moot.

The Examiner has further rejected claims 115 and 116 as indefinite as the metes and bounds of the term "stringent conditions" are not clear to the Examiner from Applicant's specification. While it is Applicant's position that an ordinarily skilled artisan would have known what was meant by the stringent hybridization conditions recited in claims 115 and 116 given the teachings of the instant specification, claim 115 has been amended to recite the specific stringent hybridization conditions of hybridization in 0.5M $NaHPO_4$ at 65°C followed by washing in 0.1xSSC at 68°C. Support for the amendment to claim 115 can be found in the specification at least, for example, at page 27, lines 14-18. Applicant respectfully submits that the instant amendment of claim 115 and cancellation of claim 116 renders this rejection moot.

The Examiner has further rejected claims 115 and 116 over the rejection of the phrase "sharing 75% identity". The Examiner states that it is unclear whether the shared identity is overall sequence identity or identity with some "portion" of the recites reference sequences. Applicant has amended claims reciting the phrase "sharing 75% identity" to further recite an algorithm for determining % identity. Applicants notes that the algorithm recited is a global alignment algorithm, clarifying Applicant's intent that sequences claimed share overall sequence identity with the recited reference sequences. In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The Examiner has further rejected claims 117-124, 129 and 132-133 over the recitation of the term "assay" stating that the term lack proper antecedent basis. Applicant respectfully points out that claim 117 does not recite the term "assay". Claim 119 has been cancelled. Moreover, claims 118, 120-124, 129 and 132-134, as amended,

no longer recite the term "assay". In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 117-124, 129 and 132-133 over the recitation of the term "assay".

The Examiner has further rejected claim 132 over the recitation of the phrases "a natural metabolite", "a synthetic chemical", "a synthetic metabolite", etc. Applicant traverses. Applicant exemplifies in claim 132 various species of the genus "candidate compound" and utilized art-recognized terms to refer to said species. The skilled artisan would readily appreciate what Applicant means by the phrases "a natural metabolite", "a synthetic chemical", "a synthetic metabolite", etc. as these are phrases routinely used in the art. As such, it is Applicant's position that recitation of the phrases "a natural metabolite", "a synthetic chemical", "a synthetic metabolite", etc. in no way renders claim 132 indefinite and respectfully requests reconsideration and withdrawal of the rejection of claim 132 under 35 U.S.C. 112, second paragraph.

The Examiner further rejects claim 133 over the recitation of the word "small". Applicant again respectfully submits that the word small, when read in the appropriate context, *i.e.*, a "small molecule" does not render claim 133 indefinite as the term is again one routinely used by the skilled artisan and has and art-recognized meaning. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 133 under 35 U.S.C. 112, second paragraph.

The Examiner further rejects claim 134 over the recitation of the phrase "from an intracellular milieu". While it is Applicant's position that, again, the skilled artisan would readily what is meant by the term intracellular milieu (without defining each component of said milieu), claim 134 has been cancelled in order to expedite prosecution

of the instant application. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 134 under 35 U.S.C. 112, second paragraph.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 115-116 stand rejected under 35 U.S.C. 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner states that claims 115-116 are directed to a genus of polypeptides, *e.g.*, "any and all polypeptides sharing at least 75% identity with the amino acid sequence of SEQ ID No: 2, polypeptides encoded by nucleic acid molecules sharing at least 75% identity with SEQ ID NO: 1, and polypeptides encoded by nucleic acid molecule that hybridize under stringent conditions with the nucleic acid molecule of SEQ ID No: 1". The Examiner is of the opinion that Applicant has not adequately described this genus. Applicant traverses.

Claim 116 has been cancelled, rendering the rejection moot with respect to this claim. Moreover, claim 115 has been amended. Amended claim 115 is directed to methods featuring cells that express a vector-derived MRP-β polypeptide having 85% overall sequence identity to SEQ ID No: 2. Certain other features of previously pending claim 115 are now recited in the new claims. The following arguments may be deemed pertinent to the extent that features of previously pending claim 115 are recited in the new claims.

Applicant first directs the Examiner's attention to the fact that claim 115 is not directed to a genus of polypeptides. Rather the claim is directed to a *method* of identifying MRP-β modulators that involves contacting a cell expressing certain MRP-β polypeptides with a candidate modulator and identifying the candidate as an MRP-β modulator based on production of a detectable fluctuation in MRP-β activity. Specifically, the cell expresses an MRP-β polypeptide having a significant degree of sequence identity to the reference MRP-β polypeptide set forth as SEQ ID No: 2. Moreover, the expressed polypeptide possesses a MRP-β activity in order that fluctuations in activity can be detected. Applicant respectfully submits that there is sufficient written description in the specification regarding the claimed methods to inform a skilled artisan that Applicant was in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see also, M.P.E.P. 2163.02).

The methods feature cells that express a vector-derived MRP-β. Cells are produced according to the methodology described at, for example, pages 33-36, using vectors produced according to the methodology described at, for example, pages 31-33, said vectors expressing MRP-β or MRP-β homologues or variants as described, for example, at pages 26-31. MRP-β homologues or variants taught by the instant specification include polypeptides encoded by nucleic acid molecules which hybridize under highly stringent conditions to a complement of the nucleic acid set forth as SEQ ID No: 1 (see *e.g.*, page 27), polypeptides having a significant degree of homology to the amino acid sequence of SEQ ID No: 2 (*i.e.*, polypeptides that differ from that comprising

SEQ ID No: 2 by the presence of one or more amino acid insertions, deletions, or point substitutions, for example, chimeric polypeptides in which one or more MRP-β amino acid residues are replaced by the corresponding residue in either the MRP or P-glycoprotein sequence) (see *e.g.*, page 31), polypeptides encoded by the cDNA insert of clone fohd013a05m (see *e.g.*, page 7) and the like. Methods for testing the biological activity of MRP-β polypeptides are taught throughout the specification and exemplified in Examples 4 and 5. The teachings described above clearly evidence that Applicant had in his possession the genus of methods of claim 115. Applicant teaches multiple host cell types for carrying out the invention, multiple expression vectors (including appropriate control elements, etc.) suitable for use in expressing MRP-β polypeptides, as well as various MRP-β homologues and variants and methods for assaying the activity of said homologues and variants. It is Applicant's position that the specification provides more than adequate description of the genus of methods of claim 115 and has provided within the instant specification representative examples of the genus as well as description of common features of the genus. In view of the above, Applicant submits that the instant specification satisfies the written description requirement for the claimed invention.

Claim 115 stands rejected under 35 U.S.C. 112, first paragraph, as being not enabled due to failure by Applicant to evidence a suitable deposit of the biological mater recited in the claim. Applicant first directs the Examiner's attention to the fact that the specification was amended by preliminary amendment to recite the name and address of the depository with which the plasmid having ATCC as Accession Number 94809 was deposited. Moreover, as required under 37 C.F.R. §1.804(b), Applicant states herein that the plasmid containing the full length nucleotide sequence of human MRP-β (clone

fohd013a05m) was deposited on April 16, 1997 with the ATCC as Accession Number 94809, and is the plasmid specifically identified at page 7 of the specification of U.S. Serial No. 09/061,400. This deposit was made under the conditions of the Budapest Treaty and complies with the preservation and public disclosure requirements of M.P.E.P. 608.01 (p) (C). Applicant further states herein, in accordance with 37 C.F.R. §1.808(a), that access to the deposit will be available during pendency of the above-referenced application to one determined by the Commission to be entitled thereto under §1.14 and 35 U.S.C. 122, that the deposit will be replaced if viable samples cannot be dispensed by the depository and that the deposit will irrevocably and without restriction or condition be released to the public upon issuance of a patent. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection of claim 115.

The Examiner has further rejected claims 106-108 and 115-134 under 35 U.S.C. 112, first paragraph, as not enabling the skilled artisan to practice the invention commensurate in scope with these claims. In particular, the Examiner has rejected the enumerated claims as not reasonably providing enablement "for identifying stimulatory modulators of MRP-β", "for the scope of modulators of claim 132", or "for identifying modulators by testing for sequestration of substrates other than cytotoxins". Claims 116, 119 and 134 have been cancelled, rendering the rejection moot with respect to these claims. With respect to the remaining pending claims, Applicant traverses the rejection and submits the following.

The Examiner cites various publications describing compounds (*e.g.*, verapamil and safingol) that *inhibit* multidrug resistance by *interfering* with multidrug resistance-

associated transporters, for example, P glycoprotein. The Examiner summarizes what the references fail to teach, *i.e.*, (1) sequestration of substrates other than cytotoxins for identifying modulators of multidrug resistance; (2) compounds that otherwise modulate (*e.g.*, stimulate) multidrug resistance; and (3) compounds corresponding in scope with "natural metabolites", "synthetic chemicals", "synthetic metabolites", "naturally sourced chemicals" or "naturally sourced secretion products". The Examiner relies on what the references fail to teach in concluding that it would require undue experimentation to carry out the claimed methods for identifying MRP-β modulators, where the methods feature assaying for transport of non-cytotoxin substrates, assaying for stimulatory compounds or assaying compounds, for example, "natural metabolites", "synthetic chemicals", "synthetic metabolites", "naturally sourced chemicals" or "naturally sourced secretion products". The Examiner appears to be of the opinion that because the references fail to teach certain formats of the claimed methods, it would require undue experimentation to practice the claimed methods.

It is Applicant's position that the assay format or test compound source selected for practicing the claimed invention is not determinative of the experimentation required to practice the claimed invention. The amount of experimentation required to test an unknown compound for a stimulatory activity does not vary considerably from the amount of experimentation necessary to test an unknown compound for an inhibitory activity. In either scenario, the unknown (or candidate) compound is contacted with the test cell and detectable fluctuation in expression or activity is assayed. Moreover, the amount of experimentation required to test a "natural metabolite", "synthetic chemical", "synthetic metabolite", "naturally sourced chemicals" or "naturally sourced secretion

product" for the ability to modulate MRP-β activity or expression does not vary considerably from the amount of experimentation required to test verapamil or safingol for the ability to modulate MRP-β activity or expression. Furthermore, the amount of experimentation required to test another substrate (*e.g.*, a cytotoxin metabolite or derivative) for transport or sequestration is no greater than the amount of experimentation required to test a cytotoxin for transport or sequestration. In any scenario, the unknown (or candidate) compound is subjected to the assay methodology and identified as a modulatory compound if a fluctuation in activity or expression is detected. The source of the compound does not significantly effect the amount of experimentation required to carry out the methods, nor does the type of substrate transported significantly effect the amount of experimentation required to carry out the methods. The invention is particularly designed to identify modulatory compounds from a wide source of test or candidate compounds and is amenable to various formats to identify inhibitory and stimulatory compounds. The specification provides sufficient guidance to the skilled artisan to carry out the invention, regardless of the source of test compound, substrate transported or modulatory effect. As the Examiner is aware, enablement is not precluded by the necessity for some experimentation (see, e.g., In re Wands 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicant respectfully submits that any experimentation that may be required to carry out the various formats of the invention constitutes routine, not undue, experimentation and therefore the specification clearly enables the pending claims.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of thes rejection of claims 106-108 and 115-134 under 35 U.S.C. 112, first paragraph.

Claim Rejections – 35 U.S.C. § 102

Claims 108, 117 118, 120, 121-123, 129 and 131-133 stand rejected as being anticipated by Solary et al. The Examiner relies on Solary et al. as teaching identification of a modulator of multidrug resistance that involves contacting a human cell with doxorubicin and verapamil and assaying for cell survival. Solary et al. teach that the mechanism of multidrug resistance involves P glycoprotein. The Examiner states, however, that P glycoprotein could be interpreted as being the same a MRP-β (due to the alleged lack of definiteness of this term as previously discussed). Alternatively, the Examiner states that Applicant's claimed method is inherent in the teachings of Solary et al. Applicant traverses.

Independent claim 108 and dependent claims 117, 118, 120, 121-123, 129 and 131-133 have been amended. As amended, the claims feature a cell that expresses "a vector-derived MRP-β polypeptide, the amino acid sequence of which shares at least 75% sequence identity with SEQ ID No: 2, as determined by the ALIGN algorithm (weight residue table = PAM120, gap length penalty = 12, gap penalty = 4)". Notably, the cell featured in the method of Solary et al. fails to express such a vector-derived MRP-β polypeptide. As such, Solary et al. fails to teach each and every element of the claimed invention and, accordingly, fails to anticipate the claimed invention. Applicant

respectfully requests reconsideration and withdrawal of the rejection of claims 108, 117 118, 120, 121-123, 129 and 131-133 under 35 U.S.C. § 102 in view of Solary et al.

Claims 106-108, 117, 118, 120, 121-123, 125-127 and 129-134 stand rejected as being anticipated by Chao. The Examiner relies on Chao as teaching identification of a modulator of multidrug resistance that involves contacting multidrug resistant B lymphoma cells with vincristine and verapamil and assaying for intracellular drug accumulation. Chao teach measuring *mdr1*, P-glycoprotein and cell survival. The Examiner states that the claims are anticipated for the same reasons as discussed in the context of the Solary et al. reference. Applicant traverses.

Claim 134 has been cancelled rendering the rejection moot with respect to this claim. Independent claims 106-108 and dependent 117 ,118, 120, 121-123, 125-127 and 129-133 have been amended. As amended, claim 106 and corresponding dependent claims feature detection of expression of the nucleic acid of SEQ ID No: 1. Claims 107-108 and corresponding dependent claims feature a cell that expresses "a vector-derived MRP-β polypeptide, the amino acid sequence of which shares at least 75% sequence identity with SEQ ID No: 2, as determined by the ALIGN algorithm (weight residue table = PAM120, gap length penalty = 12, gap penalty = 4)". Notably, Chao fails to teach detection of the nucleic acid molecule of SEQ ID No: 1 and, further, the cell featured in the method of Chao fails to express a vector-derived MRP-β polypeptide having 75% sequence identify with SEQ ID No: 2. As such, Chao fails to teach each and every element of the claimed invention and, accordingly, fails to anticipate the claimed invention. Applicant respectfully requests reconsideration and withdrawal of the

rejection of claims 106-108, 117, 118, 120, 121-123, 125-127 and 129-134 under 35 U.S.C. § 102 in view of Chao.

Claims 106-108, 117, 118 and 120-134 stand rejected as being anticipated by Sachs et al. The Examiner relies on Sachs et al. as teaching identification of a modulator of multidrug resistance that involves contacting MCF-7 cells with safingol and verapamil and assaying for intracellular drug accumulation. Sachs et al. teach measuring *mdr1*, P-glycoprotein and cell survival. The Examiner states that the claims are anticipated for the same reasons as discussed in the context of the Solary et al. reference. Applicant traverses.

Claim 134 has been cancelled rendering the rejection moot with respect to this claim. Independent claims 106-108 and dependent 117 ,118, and 120-133 have been amended. As amended, claim 106 and corresponding dependent claims feature detection of expression of the nucleic acid of SEQ ID No: 1. Claims 107-108 and corresponding dependent claims feature a cell that expresses "a vector-derived MRP-β polypeptide, the amino acid sequence of which shares at least 75% sequence identity with SEQ ID No: 2, as determined by the ALIGN algorithm (weight residue table = PAM120, gap length penalty = 12, gap penalty = 4)". Notably, Sachs et al. fails to teach detection of the nucleic acid molecule of SEQ ID No: 1 and, further, the cell featured in the method of Sachs et al. fails to express a vector-derived MRP-β polypeptide having 75% sequence identify with SEQ ID No: 2. As such, Sachs et al. fails to teach each and every element of the claimed invention and, accordingly, fails to anticipate the claimed invention. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims

106-108, 117, 118, 120, 121-123, 125-127 and 129-134 under 35 U.S.C. § 102 in view of Sachs et al.

Claim Rejections – 35 U.S.C. § 103

Claims 106-108, 115-118, 120-121 and 123-124 stand rejected as being unpatentable over Sachs et al. in view of Kool et al. The Examiner relies on Sachs et al. for the teachings described above. The Examiner relies on Kool et al. for teaching "homologues of the multidrug resistance associated protein *mrp1* which have 98.8% identity and 99.9% local similarity with the polynucleotide of SEQ ID No: 1". The Examiner concludes that it would have been obvious at the time of the invention to use the polypeptide of Kool et al. in the method of Sachs et al. to arrive at the claimed invention. Applicant traverses.

Applicant respectfully asserts that the Examiner mischaracterizes the Kool et al. reference (GenBank Accession No. U83661). In particular, the Kool et al. sequence aligned to Applicant's SEQ ID No: 1 (result #4 in the Sequence Search conducted 11/09/2001) is not art as of the submission date of January 3, 1997 but rather is art only as of the publication date of the particular record, *i.e.*, June 21, 2000. Notably, the publication of the Kool et al. sequence at issue (*i.e.*, the complete MRP-5 sequence) was well after Applicant's priority date. Applicant attaches hereto as APPENDIX B a "Sequence Revision History" for the electronic record having accession no. U83661. The Examiner will note that prior to Applicant's priority date, only an EST fragment corresponding to MRP5 was available. As the full length sequence of Kool et al. (aligned to Applicant's SEQ ID No: 1 in the Sequence Search conducted 11/09/2001) is unavailable as prior art and the EST of Kool et al. (published September 27, 1997)

contains insufficient sequence information to meet the % identity limitations of the presently pending claims, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 106-108, 115-118, 120-121 and 123-124 under 35 U.S.C. § 103.

Claims 119 and 122 stand rejected as being unpatentable over any of Solary et al., Chao or Sachs et al. in view of Raymond et al. The Examiner relies on Solary et al., Chao and Sachs et al. for the teachings described above. The Examiner relies on Raymond et al. as teaching insertion of *mdr3* into *S. cerevisiae* which confers drug resistance to the cell. Applicant traverses.

Claim 119 has been cancelled rendering the rejection moot with respect to this claim. Claim 122 is directed to the method of any one of claims 106-108 "wherein the cell is a yeast or mammalian cell". For the reasons set forth above, none of Solary et al., Chao or Sachs et al. teach the methods of amended claims 106-108. Although Raymond et al. teaches expression of *mdr3* in a yeast cell, nothing in the reference serves to rectify the deficiency in the teachings of Solary et al., Chao or Sachs et al. with regards to the MRP-β nucleic acid molecule being detected (claim 106) or the cells used in the methods featured in claims 107-108. In view of the above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 119 and 122 under 35 U.S.C. § 103.

SUMMARY

Entry into the record of the application of the foregoing claim amendments and remarks, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call (617) 227-7400.

Date: May 2, 2002

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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

The paragraph beginning at page 1, line 3, has been replaced with the following rewritten paragraph:

This patent application is a continuation application of U.S. Patent Application Serial No. 09/061,400, filed on April 16, 1998 [(allowed)] (U.S. Patent No. 6,077,936), which in turn is a continuation-in-part of U.S. Serial Number 08/843,459, filed April 16, 1997 (U.S. Patent No. 6,162,616), the [disclosure] disclosures of which [is] are incorporated herein by reference.

The paragraph beginning at page 23, line 1, has been replaced with the following rewritten paragraph:

[FIGURE 1] FIGURE 1A-G is a text representation of an MRP-β cDNA sequence and of the polypeptide sequence encoded therein, as set forth in SEQ ID Nos: 1 and 2.

The paragraph beginning at page 23, line 3, has been replaced with the following rewritten paragraph:

[FIGURE 2] FIGURE 2A-F is a text representation comprising aligned amino acid sequences of the known ABC Transporter Protein superfamily member MRP (described in Deeley et al. (1996) U.S. Patent 5,489,519), and of the novel MRP-β disclosed herein. Dashes (-) indicate gaps introduced to maximize alignment of similar sequences; colons (:) indicate the locations of identical aligned amino acid residues.

The paragraph beginning at age 35, line 5, has been replaced with the following rewritten paragraph:

The present host cells initially are expected to facilitate production of MRP-β polypeptides and structural and functional analysis thereof. The MRP-β polypeptide comprising SEQ ID No: 2 is expected to bind ATP, and to be an integral, multispanning transmembrane protein generally as described in Almquist et al. (1995), 55 Cancer Res. 102-110. A significant portion of the total MRP-β produced in host cells is expected to span the cells' plasma membrane, with an additional portion being present intracellularly, e.g., in the endoplasmic reticulum and/or the Golgi apparatus. Thus, MRP-β host cells are expected to display extracellular portions of the multispanning MRP-β polypeptide on the cell surface, appropriately configured to mediate the ATP-dependent sequestration or export (efflux) of a plurality of cytotoxic drugs, including drugs conventionally used as chemotherapeutic agents. These general properties are deduced from an assessment of the primary structure (sequence) of the MRP-β polypeptide. MRP-β is considered to be a novel member of the ABC Transporter Protein superfamily and is deemed likely to contribute to multidrug-resistance phenotypes by mediating drug transport across cellular phospholipid membranes. [FIGURE 2] FIGURE 2A-F sets forth an exemplary sequence alignment of the disclosed novel MRP-β polypeptide (SEQ ID No: 2), with relevant sequence of the MRP polypeptide of Deeley et al. (1996), U.S. Patent No. 5,489,519 (SwissProt P33527, 1531 aa). The alignment was generated using the ALIGN algorithm (which calculates a global alignment of two sequences), version 2.0 (Myers and Miller (1989) CABIOS), scoring matrix: PAM120, gap penalties: -12/-4, 30.9% identity, global alignment score: 1214.

The paragraph beginning at page 55, line 15, has been replaced with the following rewritten paragraph:

A nucleic acid probe corresponding to the SEQ ID No: 3 unique fragment was prepared by conventional techniques. This probe was used for hybridization screening of the HUMVEC expression library for the presence of MRP-β cDNAs. This procedure yielded an MRP-β cDNA (residues 67-4847 [FIGURE 1] FIGURE 1A-G and SEQ ID No: 1), 4.78 kb (kilobases) in length. The clone comprising this cDNA insert has been

designated fohd013a05m and deposited with the American Type Culture Collection. Two independent cDNA clones comprising approximately 60 residues upstream (5') from the fohd013a05m MRP-β insert were isolated by hybridization screening of human brain and liver cDNA libraries with a nucleic acid probe corresponding approximately to the 5' 0.5 kb of the fohd013a05m MRP-β insert. This probe was prepared by isolating an approximately 0.5 kb SacI fragment from fohd013a05m. The cDNA sequence presented in SEQ ID No: 1 comprises the sequence of the fohd013a05m MRP-β insert and the sequence of an additional 66 upstream (5') nucleotides. The open reading frame (ORF) of the SEQ ID No: 1 cDNA encodes an MRP-β polypeptide (SEQ ID No: 2) 1437 amino acid residues in length and in addition, includes a 0.42 kb 3' untranslated region. The ORF start site indicated in SEQ ID No: 1 (at nucleotides 116-118 of SEQ ID No: 1) is the first in-frame ATG codon downstream from the TGA stop codon at nucleotides 23-25 of SEQ ID No: 1.

In the Claims:

Claims 106-108, 115, 117-118, 120-129 and 131-133 have been amended, as follows:

106. (Twice Amended) A method of identifying a modulator of MRP-β, comprising the steps of:

(a) contacting a [MRP-β expressing] cell with a candidate modulator of MRP-β;

(b) assaying the level of [MRP-β] expression of the MRP-β nucleic acid molecule set forth as SEQ ID No: 1 in said cell, wherein a detectable fluctuation in said level indicates that said candidate modulator is an MRP-β modulator.

107. (Twice Amended) A method of identifying a modulator of MRP-β, comprising the steps of:

(a) contacting a [MRP-β expressing host] cell with a substrate [transported] exported or sequestered by MRP-β, said cell expressing a vector-derived MRP-β polypeptide, the amino acid sequence of which shares at least 75% sequence

identity with SEQ ID No: 2, as determined by the ALIGN algorithm (weight residue table = PAM120, gap length penalty = 12, gap penalty = 4);

(b) contacting said cell with a candidate modulator of MRP-β;

(c) assaying for a detectable fluctuation in export or sequestration of said substrate, a detectable fluctuation in which indicates that said candidate is an MRP-β modulator.

108. (Twice Amended) A method of identifying a modulator of MRP-β, comprising the steps of:

(a) contacting a [MRP-β expressing host] cell with a cytotoxin exported or sequestered by MRP-β, said cell expressing a vector-derived MRP-β polypeptide, the amino acid sequence of which shares at least 75% sequence identity with SEQ ID No: 2, as determined by the ALIGN algorithm (weight residue table = PAM120, gap length penalty = 12, gap penalty = 4);

(b) contacting said cell with a candidate modulator of MRP-β;

(c) assaying survival of said cell, a detectable fluctuation in which indicates that said candidate is an MRP-β modulator.

115. (Amended) The method of [any one of claims 106-108] claim 107 or 108, wherein the [cell expresses a] amino acid sequence of the vector-derived MRP-β polypeptide [selected from the group consisting of:

(a) a polypeptide comprising the amino acid sequence of SEQ ID No: 2;

(b) a polypeptide comprising an amino acid sequence sharing] shares at least [75%] 85% sequence identity with the amino acid sequence of SEQ ID No: 2[;

(c) a polypeptide encoded by the nucleic acid molecule of SEQ ID No: 1;

(d) a polypeptide encoded by a nucleic acid molecule sharing at least 75% sequence identity with the nucleic acid molecule of SEQ ID No: 2;

(e) a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent hybridixation conditions with the nucleic acid molecule of SEQ ID No: 2; and

(f) a polypeptide encoded by the DNA insert of the plasmid deposited as ATCC Deposit No. 94809].

117. (Amended) The method of [claim 107] any one of claims 107, and 138-140, wherein the substrate is a cytotoxin.

118. (Amended) The [assay] method of any one of claims [106-108] 107-108, and 138-143, wherein MRP-β expression confers a survival advantage on said cell

120. (Amended) The [assay] method of any one of claims [106-108] 107-108, and 138-143, wherein the cell expresses a cell surface MRP- β polypeptide.

121. (Amended) The [assay] method of any one of claims 106-108, and 138-143, wherein the cell is a eukaryotic cell.

122. (Amended) The [assay] method of any one of claims 106-108, and 138-143, wherein the cell is a yeast or mammalian cell.

123. (Amended) The [assay] method of any one of claims 106-108, and 138-143, wherein the cell is a human cell.

124. (Amended) The [assay] method of any one of claims 106-108, and 138-143, wherein the [host] cell is a MCF-7 cell.

125. (Amended) The method of claim 106, wherein assaying the level of MRP-β comprises assaying the amount or rate of production of MRP-β polypeptide is said cell.

126. (Amended) The method of claim [106] 135, wherein assaying the level of MRP-β comprises assaying the amount or rate of production of MRP-β polynucleotide is said cell.

127. (Amended) The method of claim 106 or 135, wherein a detectable decrease or cessation of MRP-β expression indicates that the candidate is an inhibitory modulator.

128. (Amended) The method of claim 106 or 135, wherein a detectable increase in MRP-β expression indicates that the candidate is a stimulatory modulator.

129. (Amended) The [assay] method of any one of claims 106-108, and 138-143, wherein the candidate modulator is contacted with the cell prior to, concomitantly with, or following exposure to the substrate.

131. (Amended) The method of claim 108, wherein a detectable decrease in survival indicates that the candidate is an inhibitory modulator.

132. (Amended) The [assay] method of any one of claims 106-108, wherein the candidate modulator is selected from the group consisting of a natural metabolite, a synthetic chemical, a synthetic metabolite, a toxin, an antibiotics, an element of a combinatorial chemistry library, an element of a nucleotide library, an element of a peptide library, a naturally sourced chemical, a naturally sourced cell secretion product, and a cell lysate[,] .

133. (Amended) The [assay] method of any one of claims 106-108, wherein the [candiate] candidate modulator is a small molecule.